

 pharmacological agent with a recombinant human neutral sphingomyelinase having an amino acid sequence represented by SEQ ID NO. 2 or fragment or derivative thereof and analyzing the mixture of the candidate agent and human neutral sphingomyelinase or fragment or derivative thereof, wherein the analyzing step further comprises comparing enzyme activity in the presence and absence of the agent.

✓
Please cancel claims 18-30 without prejudice.

REMARKS

Claims 18-30 have been canceled merely to conform with a prior restriction requirement. The claims were not canceled for any reason related to patentability. The right to file subsequent applications encompassing the canceled subject matter is reserved.

Claim 13 has been amended. Support for the amendment can be found throughout the instant application including the Drawings and claims as filed originally. See eg., pg. 8, lines 11-14. The amendment introduces no new matter to the application.

Claims 13 and 15-17 stand rejected under 35 USC §112, first paragraph, as not being enabled for methods involving use of a fragment or derivative of human neutral sphingomyelinase. Although Applicants respectfully disagree with the position taken at pgs. 2-3 of the Action, grounds for the rejection have been addressed .

Specifically, claim 13 has been amended along lines suggested by the Examiner. As amended, the recited recombinant N-Smase is represented by the amino acid sequence of SEQ ID NO 2. Accordingly, the fragments and derivatives featured in the claim must also be derived from that specific amino acid sequence.

In view thereof, reconsideration and withdrawal of the rejection are respectfully requested.

Claims 13-17 stand rejected as being obvious under 35 USC §103 over Chatterjee et al. (JBC (1989) 264: 12554) and Ogita et al. (WO 95/18119). Applicants respectfully traverse the rejection for the following reasons.

As acknowledged in the Action, the cited references do not provide for any method in which a recombinant sphingomyelinase enzyme is used. Action at pg. 4. In contrast, the claimed invention features a method in which that enzyme is employed. Accordingly, the Office's cited combination of references is not the claimed invention. On this basis alone, there is no *prima facie* case for obviousness and the rejection should be withdrawn.

Respectfully, the rejection fails to withstand scrutiny on other grounds.

As understood, the position taken by the Office is that the claimed invention is unpatentable because it is supposedly obvious to make a recombinant human neutral sphingomyelinase. That position is clearly at odds with decisions of the Federal Circuit and current USPTO examination practice.

For example, the Federal Circuit made it abundantly clear that prior art disclosure of a protein sequence does not necessarily render particular DNA molecules encoding the protein obvious. See eg., *In re Deuel*, 51 F.3d 1552, 1558-59, (Fed. Cir. 1995). More is needed. In the present case, the Office has not reached the threshold addressed by *Duel*. That is, it has not even cited any protein sequence of the human neutral sphingomyelinase enzyme in formulating the rejection. Nonetheless, the Office urges that obtaining that unknown sequence and the nucleic acid that encodes it would somehow be obvious. Action at 4. Respectfully, the position is completely without merit under the case law and should be withdrawn. Not even a partial protein sequence of the human enzyme has been provided. Even assuming, *arguendo*, that such protein sequence information was cited against Applicants, the instant obviousness rejection would still fail. See *In re Deuel*, Id. MPEP § 2144.09.

Moreover, reliance by the Office on knowledge of general gene cloning methods to makes its prima facie case, without more, is not sufficient to render a particular DNA molecules obvious. See *In re Bell* 51 F.3d 1552 (Fed. Cir. 1995); and MPEP § 2144.09. Thus, the position that it would somehow be obvious to obtain an unknown partial amino acid sequence of the purified human neutral sphingomyelinase and then clone the gene encoding it does not withstand scrutiny under the case law.

A worker in possession of Applicant's specification would readily appreciate the significant advantages of working with the recombinant human enzyme. None of these advantages are taught or suggested by the cited references either alone or in combination.

For example, native N-Smase has been reported to be unstable. Specification at pg. 1, lines 15-17. Prior attempts to isolate the enzyme, as discussed in the cited Chatterjee reference, have involved manipulating large quantities of urine. Specification at pgs. 2-3, bridging paragraphs. The inconvenience and hazards of working with large urine samples are understood by those working in the field. They need not be repeated here. It is enough to say that these difficulties have made it problematic to obtain a ready supply of the enzyme with reproducible activity.

In marked contrast, the claimed invention avoids these and other drawbacks by providing, for the first time, a recombinant human neutral sphingomyelinase for use in the claimed methods. Thus, for example, the claimed invention solves prior problems of working with large quantities of urine. A more reliable enzyme source can now be provided for use with the method.

Moreover, Applicant's disclosure provides for use of recombinant enzyme fragments and derivatives. Such portions of the human enzyme would be difficult, if not impossible to obtain from the native enzyme cited in the Office Action.

None of these significant advantages provided by Applicant's invention are taught or suggested by the cited references.

As discussed in Applicant's previous response, Ogita et al., as cited, does not disclose inhibitors of the recombinant human neutral sphingomyelinase. In support, Applicant will provide a complete English translation of the document for consideration by the Examiner. That translation of Ogita et al. will be provided under separate cover.

In view thereof, reconsideration and withdrawal of the rejection are requested.

Early consideration and allowance of the application are earnestly solicited.

If for any reason a fee is required, a fee paid is inadequate or credit is owed for any excess fee paid, you are hereby authorized and requested to charge Deposit Account No. **04-1105**.

Attached to this submission is a marked-up version of the changes made to the specification and claims. The attached page is captioned "version with markings to show changes made".

Respectfully submitted,



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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Claim 13 has been amended as follows:

13. (Amended) A method of identifying a compound useful in the diagnosis or treatment of a human neutral sphingomyelinase related disorder, comprising contacting a candidate pharmacological agent with a recombinant human neutral sphingomyelinase having an amino acid sequence represented by SEQ ID NO. 2 or fragment or derivative thereof and analyzing the mixture of the candidate agent and human neutral sphingomyelinase or fragment or derivative thereof, wherein the analyzing step further comprises comparing enzyme activity in the presence and absence of the agent.

Claims 18-30 have been cancelled, without prejudice.

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